SOFTENING OF THE SPINAL CORD IN A SYPHILITIC AFTER AN INJECTION OF SALVARSAN.

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This is mainly an anatomical supplement to a purely clinical account which Dr. Victor G. Vecki has published[1] of a young man who became paralyzed in the lower extremities after an injection of salvarsan.

Dr. Vecki relates that the patient, who was aged twenty-three years, had received at the hands of another physician from June 1 to September 3, 1908, a series of intramuscular injections of corrosive sublimate for a syphilitic roseola which had followed upon a typical indurated ulcer. On March 24, 1910, Dr. Vecki, discovering a cutaneous syphilid and extensive adenitis, treated him again with injections of bichloride of mercury. These were repeated on six successive days; then, instead of them, he was given two injections of salicylate of mercury, a week intervening between these. After this the patient did not return until May 30, 1911. It is not clear why he did come back. Dr. Vecki writes that, with the exception of swollen glands, there were no manifestations of syphilis at that time. He makes no mention of a Wassermann test. However, on June 10, at noon, 0.3 gram salvarsan was injected into each buttock. On the evening of June 12, having felt perfectly well in the intervening fifty-six hours, the man first felt a numbness in his legs, then great fatigue in them, and soon after had difficulty in urinating. Throughout the day of June 13 his condition grew worse until the power of motion in his lower extremities was almost abolished and sensibility was impaired below the level of the navel. By June 14 the paraplegia was complete in every respect.

I saw the patient with Dr. Vecki and Dr. Krotoszyner four times between June 24 and July 20, 1911. His paralysis was very flaccid. The knee jerks, at first faint and hard to elicit, after a few days became a little more active, then again sluggish, and finally, very feeble again, the presence of the right one being at first and at last quite doubtful. The heel reflex could not be obtained at any time. The plantar reflex, which at the first examination could not be provoked at all, later reappeared as an extensor response and continued so. There was no abdominal reflex. The upper border of the region of altered sensibility was irregular, tactile hypoesthesia beginning in front at about the seventh rib on the right side and on the left at the level of the umbilicus. The dulness of sensation shaded downward into profound anesthesia. Sensibility to thermic and painful stimuli was affected up to somewhat lower levels. The patient's condition precluded an exact determination of the upward extension of the anesthesias. His bladder and rectum were completely paralyzed, he had numerous bed sores and other trophic disorders, and much fever. Neither mercury nor iodid nor an intravenous injection of 0.6 gram salvarsan had any influence on his state and he succumbed August 29, 1911.

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[1] California State Jour. of Med., May, 1912.

With the assistance of Dr. W. F. Beerman the spinal cord was cut up and the sections stained in the Neuropathological Laboratory of the San Francisco Polyclinic.

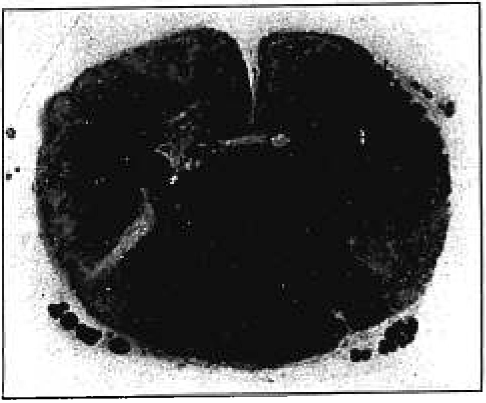

Fig. 1.—Section at upper level of softening, showing involvement of the postero-lateral region, and the anterior column on both sides, while the antero-lateral area is involved on one side only.

Pathological Anatomy. Weigert's stain for the myelin sheath shows disintegration of the myelin and softening of the cord in the fourth and fifth thoracic segments. The destruction is nowhere quite symmetrical. At the upper level of the softening the postero-lateral region (containing the crossed pyramidal tracts) is affected on both sides, and so is the anterior column, but the antero-lateral area is involved only on one side (Fig. 1). Then in a section a little lower only a small area of myelin degeneration is found in the antero-lateral column of one side. This is followed by the destruction of nearly all the myelin on one side from the postero-lateral region forward to the anterior column, while on the other side of the cord the affection of the myelin is limited to a small focus at the ventro-median corner of the anterior column (Fig. 2). At a distance of about 5 mm. below the section shown in Fig. 2, the disease becomes nearly symmetrical; ventralward from

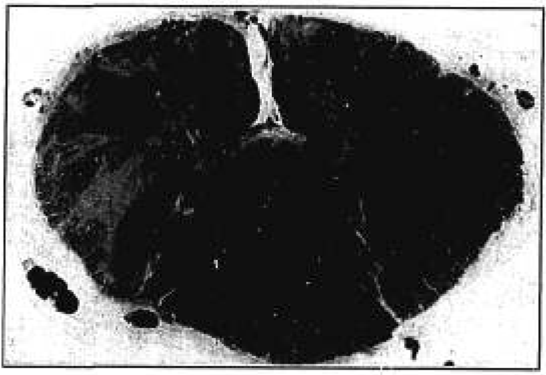

Fig. 2.—This section shows destruction of nearly all the myelin on one side from the postero-lateral region forward.

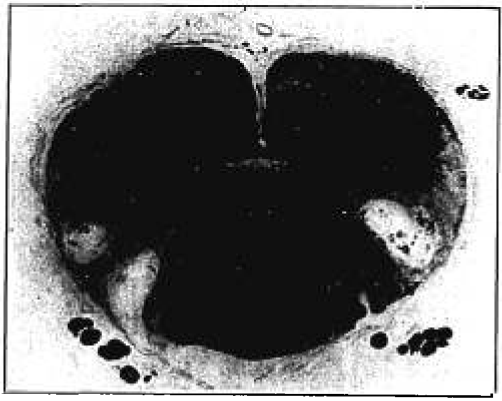

Fig. 3.—In this section of cord the disease is nearly symmetrical. In both postero-lateral areas softening has resulted in cavity formation.

the posterior horns it now spares only the white matter adjacent to the anterior horns; in both postero-lateral areas the softening of the cord has resulted in the formation of cavities (Fig. 3). Continuing the descent two small symmetrical foci of myelinic degeneration are found at the dorsal periphery of the columns of Goll next to the posterior median septum in a section which differs otherwise principally in the absence of perforations from that last described; and finally, there is a cavity again in the posterolateral region, but only one one side.

The process of breaking up of the myelin is evidently a recent one. The fragments of myelin form bodies of various sizes, ranging from large irregular masses, and drops, down to dust-like granules, either free or contained in large round cells, the granule cells.

The morbid change is more advanced in the posterolateral columns than in the anterior. The perforation of the section is not observed in the latter. The Van Gieson method enables one to trace the steps in the dissolution of the tissue. There is, for instance, a focus in one anterior column in which the disappearance of the myelin sheath is the most conspicuous result of the disease; many axis cylinders have also disappeared, those which remain are naked; the neuroglia still persists, and in its meshes is a good deal of amorphous or finely granular material. In another focus, in the opposite anterior column, the neuroglia is vanishing, one can see neuroglial fibers break off after entering the focus from the surrounding tissue. Dorsalward in the lateral columns the tissue takes less and less of the stain, large, faintly stained, round bodies (granule cells) become more numerous, there is but a trace of the neuroglia and finally this disappears in the necrosis and liquefaction of the substance of the cord in the postero-lateral region. Nowhere is any tendency to repair visible.

The gray matter shows no loss of nerve fibers. There is congestion here and there as shown by the numerous vessels engorged with blood and by occasional hemorrhages. Not only in the gray matter within the segments which show softening, but also in other parts of the cord more or less perivascular infiltration with round cells may be seen. This is also the case in the white substance, and in one place in the column of Goll, between the seventh and eighth thoracic segments, the accumulation of round cells about two capillary vessels filled with blood has assumed such proportions as to be discernible to the naked eye in the form of a speck in the mounted section (Fig. 4). This section was submitted to Professor Ophlüs, of Stanford University, and his opinion requested as to whether this formation could be regarded as a miliary gumma. He declined to apply that term to it himself, but allowed that some pathologists would probably so-call it.

The meninges are in many parts normal, or but moderately thickened, with proliferation of round cells only in a few places; but at one spot, at the lateral periphery of the cord, near an area of extreme softening the pia mater is very much thickened and infiltrated. At this place some of the dura mater is comprised in the section, and accumulations of round cells are found in the subdural fat.

In some sections the thickened pia closes the opening into the anterior sulcus, and the pia which dips into this sulcus often exhibits proliferation of round cells.

In the softened areas of the cord, bloodvessels with more or less thickened walls may be seen, but the most conspicuous vascular changes are observed in the pia-arachnoid throughout the whole length of the cord, being by no means confined to the softened segments. There are vessels which are thickened in all their coats and are completely obliterated, and now form round solid bodies of wavy connective tissue with a moderate amount of round-cell infiltration. In others the lumen is clogged by the proliferated endothelium and the wall of the vessel is thickened. In many a very small opening remains which contains blood corpuscles. The elastica of the diseased vessels does not show the resistance so often pointed out in illustrations of the syphilitic changes in arteries and veins. Weigert's elastica stain demonstrates that it is severely affected; it is distended, sometimes irregularly, or split, or broken up, and often, if at all visible, its faint fragments can be detected only when highly magnified and they remind one then of the brittle remains of worn-out rubber bands. There

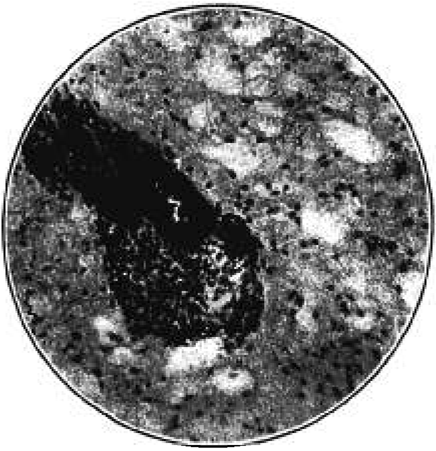

FIG. 4.—Section of cord between the seventh and eighth thoracic segments, showing accumulation of round cells about two capillary vessels.

is a very sharp contrast between these vessels and the numerous vessels adjoining or surrounding them which exhibit a deeply

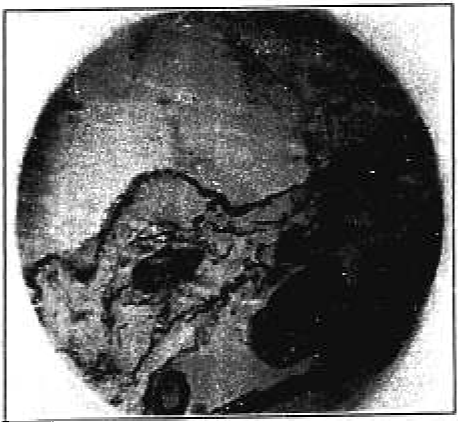

Fig. 5.—At the bottom of this section a normal meningeal artery is shown, and above it an occluded vessel.

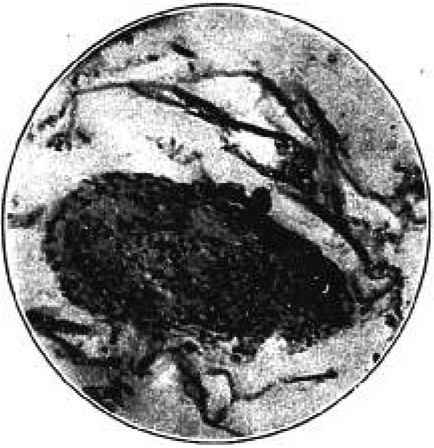

Fig. 6.—The occluded vessel seen in Fig. 5 under higher magnification.

stained normal elastica and also in other respects appear normal. These normal vessels are nearly all arteries, normal veins are far less common, and there is much reason to assume that the diseased vessels are mainly veins. Fig. 5 shows (at the bottom) a normal meningeal artery and above it an occluded vessel. Fig. 6 shows the occluded vessel under a higher magnification. The photographs are of a Van Gieson section adjacent to the Weigert section shown in Fig. 2. The vascular changes are found generally more in the dorsal part of the membranes than in that surrounding the cord on its lateral and ventral aspects, but in the lumbar region some ventral and lateral vessels are usually affected. No changes were seen in the membranes which cover the medulla oblongata.

Moderate secondary degeneration is detected by Weigert's myelin stain and also by the Marchi method in the columns of Goll and of Gowers and in the direct cerebellar tract; secondary descending degeneration in the pyramidal tracts does not appear at all in the Weigert hematoxylin sections, and in the Marchi specimens in only a very slight degree.

The gist of the foregoing is that a man who had been infected with syphilis three years before, presented the first symptoms of a fatal softening of the cord fifty-six hours after an injection of salvarsan. Was the salvarsan in any way to blame for the condition which followed its injection?

Samuel Johnson wrote more than one hundred and fifty years ago: "It is incident to physicians, I am afraid, beyond all other men to mistake subsequence for consequence." The problem of discriminating between *post hoc* and *propter hoc* continues to haunt us with all its perplexities, and in the case before us it is exemplified anew.

It is the rather close sequence of drug and disaster that impresses us with a sense of cause and effect. But opposed to the assumption of such a relation there is the clinical knowledge that acute syphilitic spinal paralysis occurred not uncommonly within three years after the infection before the introduction of salvarsan. Moreover, regarding the case from the anatomical side, it may be confidently asserted that a pathologist who might examine the specimens in this case, upon seeing the softening, the localized meningitis, the perivascular infiltration, and the widely disseminated vascular occlusions would first inquire after syphilis as an etiological factor, and, finding it, would have no occasion to seek farther. Thus clinically and anatomically the evidence in favor of the sufficiency of syphilis to produce the disease of the cord seems complete, and there would appear to be no room for the intervention of salvarsan. Even the argument which would still insist upon the striking order of events might be met, with a semblance of refutation, by an appeal to records of cases in which signs of serious damage to the central nervous system have supervened upon an injection of mercury. Thus a patient of Collins and Taylor,[2] who had had previously no sign of disease of the brain or cord, received one day, about six months after infection, an injection of mercury, felt the next day a numbness in the right leg, which he attributed to the injection, and at the end of a few days was paraplegic.

Of course, long use of mercury has taught us that no such effects are to be apprehended from it. But the comparatively brief experience with salvarsan has not permitted such a sense of security. A growing list of affections of the cranial nerves, the brain, or the spinal cord, subsequent to the administration of salvarsan will not let the suspicion die that we have to deal with a consequence of the remedy. Consider, for instance, the case reported by A. Westphal[3] of a tabetic woman who died seven hours after an intramuscular injection of 0.4 gram of salvarsan. The postmortem examination showed syphilitic changes in the cervical cord and in the cervical anterior roots which contain fibers of the phrenic nerve. Take, furthermore, the case reported by Juliusberg and Oppenheim[4] whose patient received two intravenous injections of salvarsan, each of 0.4 gram within six days, about three months after the infection, while the primary lesion was still present and swarming with spirochetes. Four days after the second injection this patient was seized with spastic paresis of the lower extremities, disturbance of sensibility, and complete paralysis of the bladder and rectum. As improvement ensued upon the treatment with mercury and iodid it was concluded that the disease of the cord was syphilitic.

When subsequences repeat themselves with some degree of uniformity they come to be looked upon as consequences. Hence that which with good reason might be interpreted in Dr. Vecki's case as a mere coincidence, when this case is considered by itself, assumes in conjunction with other similar observations the importance of a consequence. It must, therefore, be admitted after all that the salvarsan was somehow an agent in the final result.

The Herxheimer reaction has been adduced to explain such effects of salvarsan. The symptoms are supposed to be produced by a reaction in syphilitic tissue; syphilis seems to be indispensable for such action of salvarsan as we are considering. The drug appears to have a determining or precipitating or energizing influence upon syphilitic processes, perhaps identical with the influence upon which its remedial action depends. But there seems to be little or no reason to apprehend a direct noxious operation upon nervous tissue unaffected by syphilis. In this connection I may mention that in some cases of tumor of the brain and in the spinal canal under my observation, which owing to a misleading positive Wassermann reaction were treated with salvarsan, no deleterious results occurred, although the cases are too few to impart the confidence derivable from a larger number. Moreover, F. Epstein,[5] in the course of a discussion of the effects of salvarsan upon the eye, refers to the absence of nervous disturbances in the many patients who have been treated with salvarsan for malaria and other non-luetic diseases, and he quotes especially a report on 700 cases of frambœsia tropica in which no mention is made of any injury to the nervous system.

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[2] AMER. JOUR. MED. SCI., 1909, cxxxvii, 216.

[3] Berlin. klin. Woch., 1911, xxviii, 976.

[4] Münch. med. Woch., 1911, lviii, 1558.

To Dr. D'Arcy Power, of the San Francisco Polyclinic, I am indebted for his kindness in photographing the microscopic sections.

BANTI'S DISEASE AND ALLIED CONDITIONS.

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As a result of nearly thirty years' study, Banti,[1] a Florentine pathologist, recorded his investigations in a recent paper, summarizing his conclusions, previously published in various journals, as to the nature of the disease which bears his name. This disease, though not frequent, has called forth a deal of discussion; and any one who sets out to peruse the literature is at times bewildered if not totally discouraged, as pathologists, clinicians, and surgeons are sadly at variance as to the very existence, not to speak of the nosology, etiology, pathogenesis, and pathology of the disease. At the outset it may be stated that although it seems ill-advised to include under the name of Banti's disease any case which does not conform to the tenets set down by Banti himself, the impartial critic is bound to confess that any contribution to a subject in the making, like the one under discussion, is welcome if it is made with the requisite thoroughness of observation, so that its results may count in determining the status of a disease which, to say the least, it is difficult to delimit. It is to be deplored that many of the cases which are brought to bear on this subject are incompletely recorded, and that their pathological histology has received such scant attention. Since Osler[2] first drew the attention of the profession to the subject American and English clinicians have shown interest in the disease and its allied conditions.

Banti's disease is a primary splenomegaly of unknown origin;

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[5] Berlin. klin. Woch., 1911, xlviii, 2328.

[1] Folia Hæmatologica, Part I; Archiv, x, 33. See also Ziegler's Beiträge, 1898, Band iv, p. 21.

[2] Amer. Jour. Med. Sci., 1900, cxix, 54, and 1902, cxxiv, 751.